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TITLE: A Randomized, Controlled Trial of Intranasal Oxytocin as an Adjunct to Behavioral Therapy for Autism Spectrum Disorder

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14. ABSTRACT
The primary objectives of this clinical study are test the hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions, and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD), and to examine whether neuroimaging measures of brain function and structure can predict CBT treatment response. To examine these questions, we will recruit and carefully characterize 150 men, ages 18-40, with ASD to participate in this study. Participants will be randomized to receive either social skills training or a stress management/relaxation therapy, and will be randomized to receive either intranasal oxytocin or placebo. Participants and evaluators will be blind to treatment condition. In year 1 of the study, we set up the study framework, including submitting applications for approval from the MGH and MIT Internal Review Boards, and the HRPO. We also received an IND from the FDA for the use of the oxytocin, trained study staff, and began setting up recruitment efforts. The study was approved by the HRPO in April 2014, and we initiated study procedures at this time. To-date, we have enrolled 52 participants, have completed neuroimaging with 31 participants, and have randomized 35 participants into treatment. There are no study findings to report at this time, as the study is ongoing.

15. SUBJECT TERMS
autism spectrum disorder, young adult, cognitive-behavioral therapy, social skills training, oxytocin, placebo-controlled, double-blind, clinical trial

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1. Introduction

The primary objectives of this clinical study are test the two hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD). A third objective is to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness. To examine these important research questions, we will recruit and carefully characterize 100 men, ages 18-40, with ASD to participate in this study. These will all be high-functioning patients with IQ scores in the average-to-above average range (90 and higher). We will randomly assign ASD volunteers into three groups, with stratification (equation) on age, ASD severity (ADOS score), and non-verbal IQ so that the three groups are equated on those important dimensions. The three groups are: (1) Group 1 (*All Placebo*), who will receive an active placebo behavioral treatment of 12 sessions of relaxation training, and placebo medication; (2) Group 2 (*CBT/placebo*), who will receive the experimental CBT 12-session treatment, and placebo medication; and (3) Group 3 (*CBT/OT*), who will receive the experimental treatment, and OT before 12 sessions of CBT treatment. Volunteers (patients) and evaluators will be blind to condition assignment (double-blind design). We will test the *hypothesis* that CBT helps ASD adults by statistically comparing Groups 1 and 2 on outcome measures (the inclusion of medication placebo equates expectancy effects across the two groups). We will test the *hypothesis* that OT enhances CBT effectiveness in ASD adults by statistically comparing Groups 2 and 3 on outcome measures. We will perform functional (fMRI) and structural (MRI) imaging with all participants prior to treatment, and will examine the relations between measures of brain function and structure with improvements on outcome measures.

2. Keywords

autism spectrum disorder; young adult; male; cognitive-behavioral therapy; social skills training, stress management, oxytocin, placebo-controlled; double-blind; clinical trial

3. Accomplishments

a. What were the major goals of the project?

Specific Aim 1: Recruit and Clinically Characterize 150 Males Ages 18-40 with ASD
Specific Aim 2: Random, Stratified Assignment to Three Groups in a Double-Blind, Placebo Controlled Clinical Trial Design
Specific Aim 3: Use of Neuroimaging to Predict Response to Treatment

b. What was accomplished under these goals?

Specific Aim 1: We have conducted telephone screens with 82 interested individuals and enrolled 52 males with ASD into the study.

Specific Aim 2: We have randomized 35 participants into treatment. Thus far, 25 individuals have completed the study treatment.
Specific Aim 3:

- Thirty one individuals scanned prior to treatment. Of these individuals, 5 completed the scanning protocol partially
- Extracted behavioral data, converted dicoms to analysis format, for all subjects scanned to date we have completed structural image edits for Freesurfer processing stream, and preliminary analysis of functional task activation to verify data quality and expected observations.
- Completed three rounds of NDAR Data submission process. Fourth round of submission of behavioral data, image data currently being curated for submission.

c. What opportunities for training and professional development has the project provided?

Training of technical assistant in preparation of experimental paradigm. This included learning how to morph images using control points, and integrate into a Psychopy stimulus presentation script. Personnel also learned to use Nipype scripts to simplify data conversion and analysis. Research Assistants have been trained to administer cognitive assessments to every participant at baseline, broadening their experience as psychometricians. We have also involved postdoctoral fellows in psychology as clinicians in the study. These fellows are experienced in treating individuals using cognitive-behavioral therapy, and their participation in the study is an excellent opportunity to extend their skills to a more novel population. Finally, the study has employed a postdoctoral fellow at the MIT site to help run the neuroimaging scans.

d. How were the results disseminated to communities of interest?

Both MGH and MIT completed initial submissions to National Database of Autism Research (NDAR) in July 2015, January 2016, and July 2016. College and University disability services centers have been contacted and informed of study protocol and treatment opportunities with several expressing interest in establishing a working relationship between our study and their center. Clinicians in the Massachusetts General Hospital

network who have patients who were diagnosed with Autism Spectrum Disorders were contacted and informed of study protocol in the event their patients needed further treatment. This research study was posted on the autism speaks website (an organization of networked support for individuals and families with autism spectrum disorders), and disseminated at autism-related conferences such as the Daniel W. Rosenn Annual Asperger/Autism Network (AANE) Connections Conference. We have also participated in workgroups at MGH for oxytocin-related research. Finally, Drs. Gabrieli, Joshi, Wozniak, and Henin have presented at a yearly conference for professionals interested in autism spectrum disorders, hosted by the MGH Psychiatry Academy in Boston, MA. Their presentations included information directly related to the study, including the psychopharmacologic and psychosocial treatment of individuals with ASD, and neuroimaging findings in ASD.

e. What do you plan to do during the next reporting period to accomplish these goals?

During the next reporting period, we will achieve the following goals:

- Conduct weekly staff meetings with study staff to review study progress, discuss clinical issues, and avoid rater/clinician drift
- Continue study recruitment enrollment of study participants
- Continue baseline assessment and neuroimaging protocols
- Continue randomization to treatment and implement treatment protocols
- Continue week 4, week 8, and week 12 assessment protocols
- Continue data MR data collection
- Continue imaging data analysis on a subject-by-subject level (individual imaging data).
- Continue data analysis of MRI-data on individual level (including, e.g., converting dicoms to analysis format, performing structural image edits for Freesurfer processing stream, analysis of functional task activation, analysis of diffusion-weighted images)
- Start group analyses of neuroimaging data once sample size is sufficient
- Relate behavioral and imaging data (pre-treatment) with treatment outcome measures

4. Impact

a. What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

b. What was the impact on other disciplines?

Nothing to Report

c. What was the impact on technology transfer?

Nothing to Report

d. What was the impact on society beyond science and technology?

Increased awareness of treatment options for autism currently being evaluated.

5. Changes/Problems

a. Changes in approach and reason for change

We amended our telephone screen procedure to include three additional questions asked when scheduling the first appointment: the participant's full name (as it appears on their birth certificate), if they have a middle name(s), and their city of birth. This information was included to allow data coordinators to regularly match and/or create global unique identifiers for use with the National Database of Autism Research. This information is only collected if the individual decides to enroll in the study and has scheduled an initial appointment, and is stored securely in a locked file, as it has been throughout the study. This change was approved on October 13th, 2015.

We changed our intranasal oxytocin/placebo administration protocol to allow for the flexibility to have participants come twice per week for some of their treatment sessions (including both oxytocin/placebo spray nasal spray and therapy). This exception was put in place for an individual case and is intended to be used only in cases where the participant discloses extenuating circumstances which preclude him from completing the protocol in the once per week timeline. We plan to co-vary the number of weeks of treatment in the final analysis if it is a confound and will report the range of treatment duration in the final manuscript. This change was approved and went into effect on December 18th, 2015.

We introduced a new adaptive-functioning measure, the Adaptive Behavior Assessment System, Third Edition (ABAS-3) to be completed at baseline, week 4, week 8, and week 12. The inclusion of the ABAS is with the intention to collect data on adaptive functioning through self-report, as the ABAS-3 measures adaptive skills across the life span (e.g. communication, home living, self-care). The adult form which is being used is designed for individuals ages 16-89 with developmental delays, including autism spectrum disorder.

Specifically, the ABAS is intended to compliment our current measure of adaptive functioning, Vineland Adaptive Behavioral Scale, Second Edition, which is administered to parents. In many cases adult participants do not have a parent available to participate; in others, parents fail to complete the Vineland at each time period. The self-report ABAS-3 addresses the participants who fall under the latter category while also enhancing our multi-informant approach. This change went in to effect on February 8th, 2016.

We were forced to amend our protocol and patient timeline to allow participants to complete the MASC computer behavioral task at the MIT site during the baseline portion of the study. The computer that the MGH site was using to run the behavioral tasks was upgraded due to technical problems. This switch created issues with running the MASC video-based task only; however, the MASC was still able to be run on the hardware located at the MIT site. As such, the MASC was shifted to be included after the neuroimaging component at baseline and ADOS at post-treatment. This did not alter the burden significantly, as the task takes a total of 15-20 minutes to complete. This change was approved on March 30th, 2016.

b. Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to Report

c. Changes that had a significant impact on expenditures
Nothing to Report

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

e. Significant changes in use or care of human subjects
Nothing to Report

f. Significant changes in use or care of vertebrate animals
N/A

g. Significant changes in use of biohazards and/or select agents
Nothing to Report

6. Products

a. Publications, conference papers, and presentations

i. Journal publications

Henin A, Berman N. The promise and peril of emerging adulthood: Introduction to the special series. Cognitive and Behavioral Practice. 2016 Aug 23(3): 263-412.

ii. Books of other non-periodical, one-time publications

iii. Other publications, conference papers, and presentations

Henin, A (October, 2016). The promise of oxytocin as an intervention for individuals with autism spectrum disorders (as part of the symposium “Novel Strategies for Enhancing CBT”). Presented at the 50th annual convention of the Association for Behavioral and Cognitive Therapies, New York, NY.

b. Website(s) or other Internet site(s)
We initially posted our trial on clinicaltrials.gov in July 2013 and have been updating every six months. The webpage was last verified September 2016.

c. Technologies or techniques
Nothing to Report

d. Inventions, patent applications, and/or licenses
Nothing to Report

e. Other products

- Data or databases - The data from the project are being submitted to the National Database for Autism Research.

- Audio or video products - We have developed a set of novel video stimuli for investigating the emotional and cognitive reactivity of the brain. These will be made available together with the experimental paradigm scripts (see next).
- Software - We have developed a set of scripts for our novel experimental paradigm. In addition, analysis scripts are being created that can be used generally across different projects. These analysis scripts are available as part of the Nipype project. The experimental paradigm scripts will be made available alongside the publication of results.

7. Participants & Other Collaborating Organizations

a. What individuals have worked on the project?

Name:	*John D.E. Gabrieli*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*orcid.org/0000-0003*-1158-5692
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Gabrieli has provided overall supervision of the project.*
Funding Support:	*MIT*

Name:	*Aude Henin*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Henin has provided direct supervision and coordination of the project.*
Funding Support:	*MGH*

Name:	*Satrajit S. Ghosh*
Project Role:	*Principal Investigator (subaward)*
Researcher Identifier (e.g. ORCID ID):	*http://orcid.org/0000-0002-5312-6729*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Ghosh has overseen the execution of the imaging subcomponent, including experimental design, data acquisition, analysis, and submission to NDAR.*
Funding Support:	*MIT*

Name:	*Dorit Kliemann*
Project Role:	*Postdoctoral Researcher*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	*Dr. Kliemann has been involved in the execution of the imaging subcomponent, experimental design, data acquisition, analysis and submission*
Funding Support:	*Feodor Lynen Postdoctoral Fellowship of the Alexander von Humboldt Foundation , MIT, Simons Foundations Seed grant (independent to this project)*

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. John Gabrieli received an award as Co-PI (with Dr. Whitfield-Gabrieli) from the NIMH (Grant U01MH108168). This multisite study examines the neural underpinnings of mood and anxiety in adolescents.

It continues and expands the collaboration that was initiated in this project, as both Dr. Ghosh and Henin are co-Investigators on this award.

c. What other organizations were involved as partners?

i. Organization name

Massachusetts Institute of Technology (MIT)

ii. Organization Location

77 Massachusetts Avenue
Cambridge, MA 02139

iii. Partner's contribution to the project

- **Financial support** - Internal support to oversee and execute the project
- **Facilities** - Siemens Magnetom Trio 3 Tesla scanner and High Performance Computing Cluster at the McGovern Institute for Brain Research. The scanning facilities are provided by the Athinoula A Martinos Center for Biomedical Imaging at MIT.
- **Collaboration** - The staff at MIT work closely with the MGH staff on recruitment and scheduling, institutional review board updates, and preparation of project reports.

8. Special Reporting Requirements

a. Collaborative awards

Nothing to Report

b. Quad charts

Nothing to Report

9. Appendices

N/A